Metastatický triple negativní karcinom prsu

Petra Tesařová, Onkologická klinika VFN a 1:LF UK, Praha

DISCLOSURE

Consulting and advisory activity:

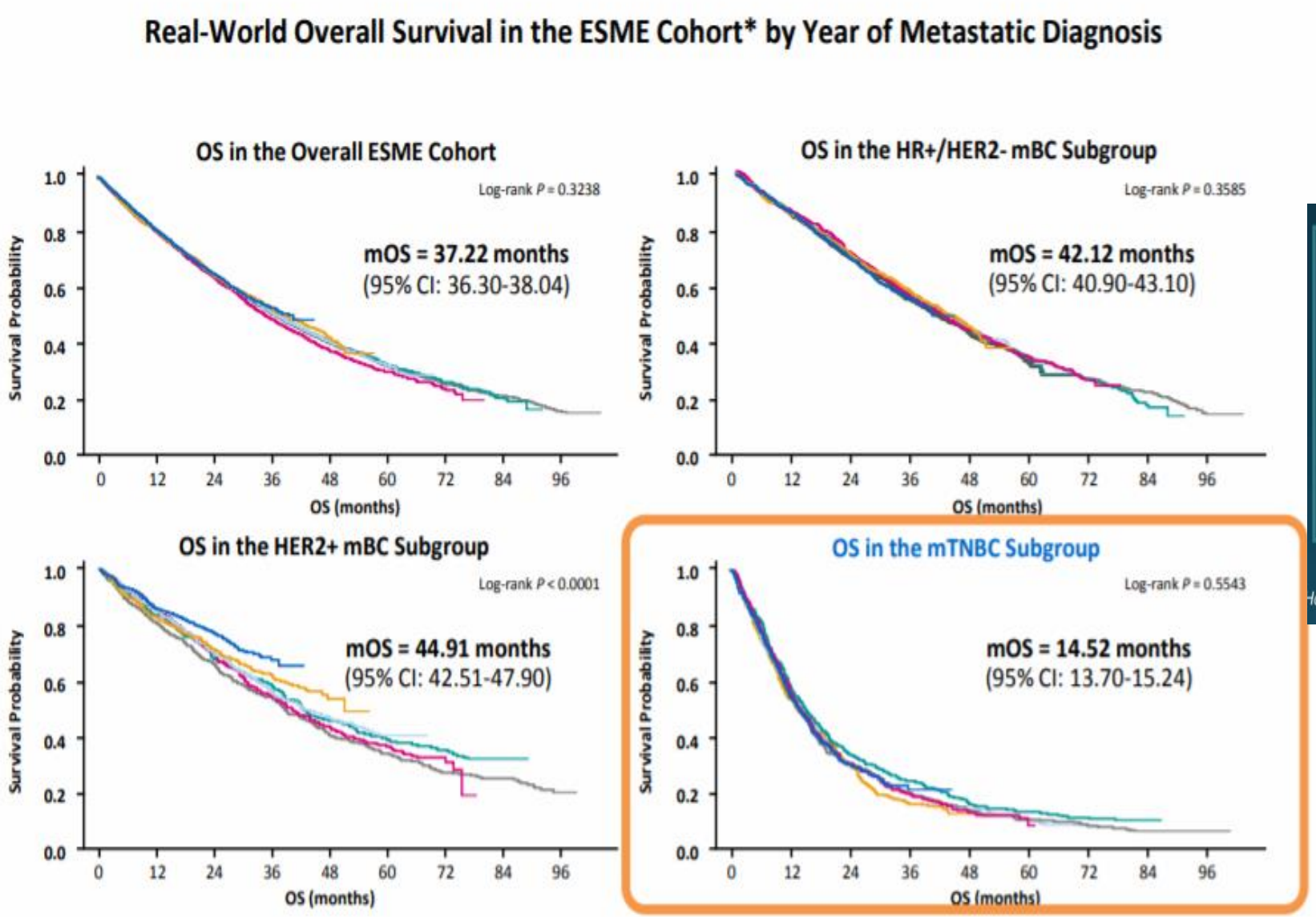
Pfizer, Novartis, AstraZeneca, Eli Lilly, Pierre Fabre, Gilead, Swixx, Sanofi

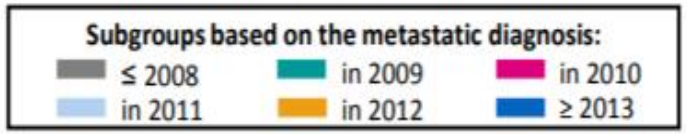
Grant/Research funding:

AstraZeneca

Nevlastním žádné akcie farmaceutických společností

Špatná prognóza TNBC se v čase nemění- nejhorší OS





- Between 2008 and 2016, no

Name	HR	HER2	Surv/4y
Luminal A (73%)	+	-	92.5%
Luminal B (11%)	+	+	90.3%
HER2 enriched (4%)	-	+	82.7%
Triple Negative (12%)	-	-	77.0%

Howlader N, Cronin KA, Kurian AW, Andridge R. Cancer Epidemiol Biomarkers Prev. 2018 Jun; 27(6):619- 62

significant unmet need for patients with mTNBC

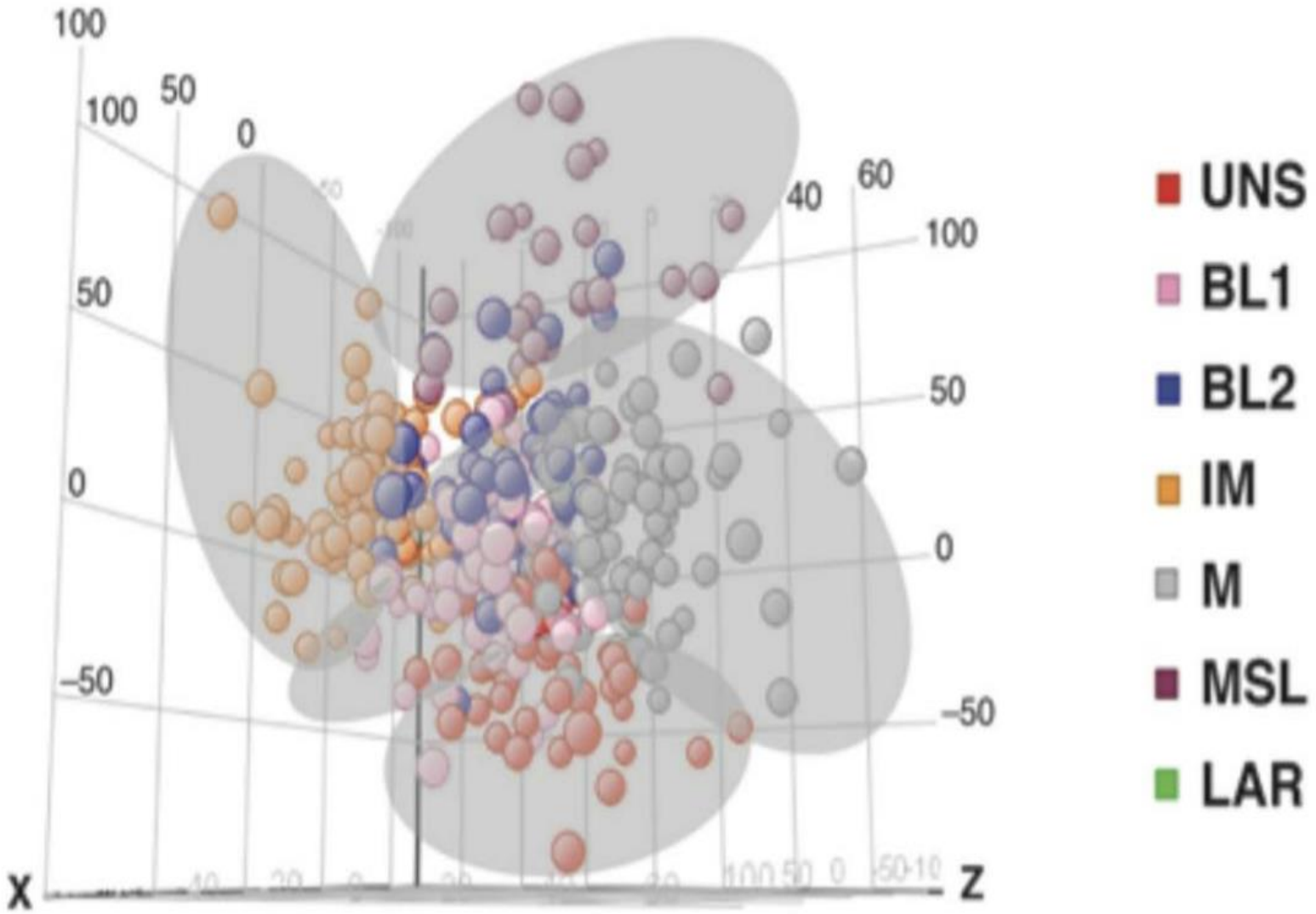
OS for patients with mTNBC is markedly lower than for patients with other mBC subtypes

Gobbini E, et al. Eur J Cancer. 2018;96:17-24.

Chybí cíl

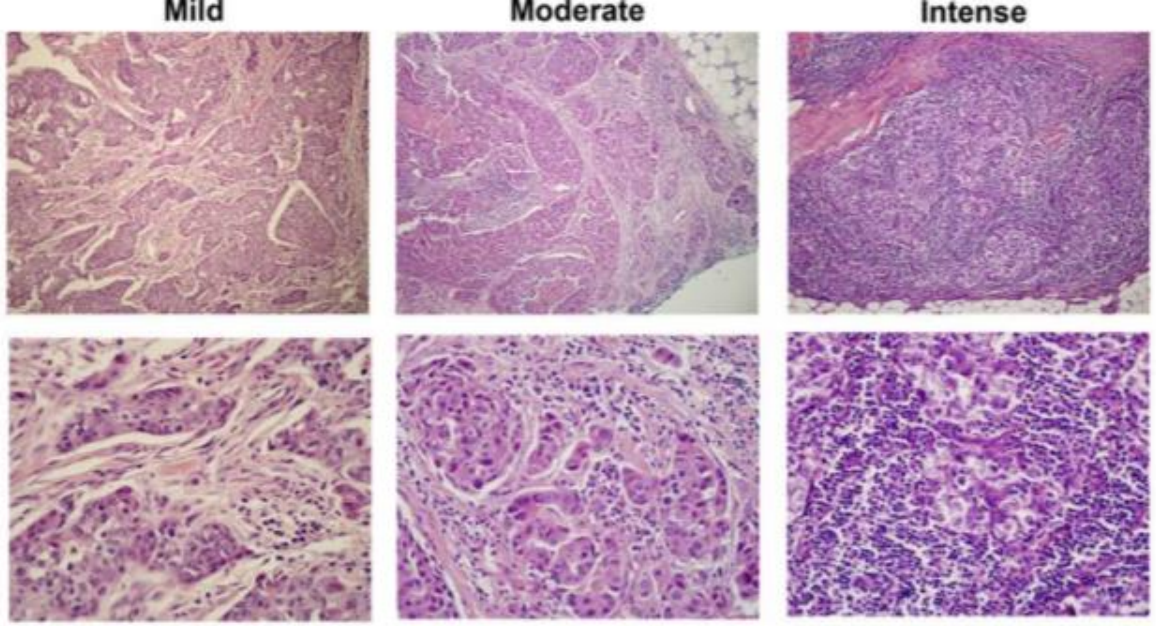
Rivenbark A et al. Am J Pathol,183:1113-24, 2013

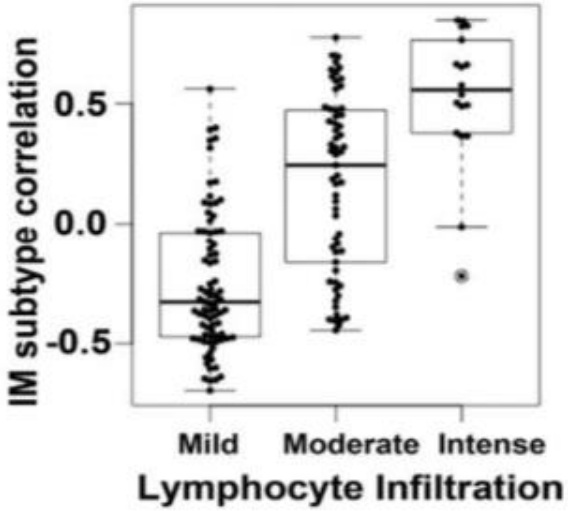
Heterogenita (N-587, 6 subtypů s unikátní genovou expresí)

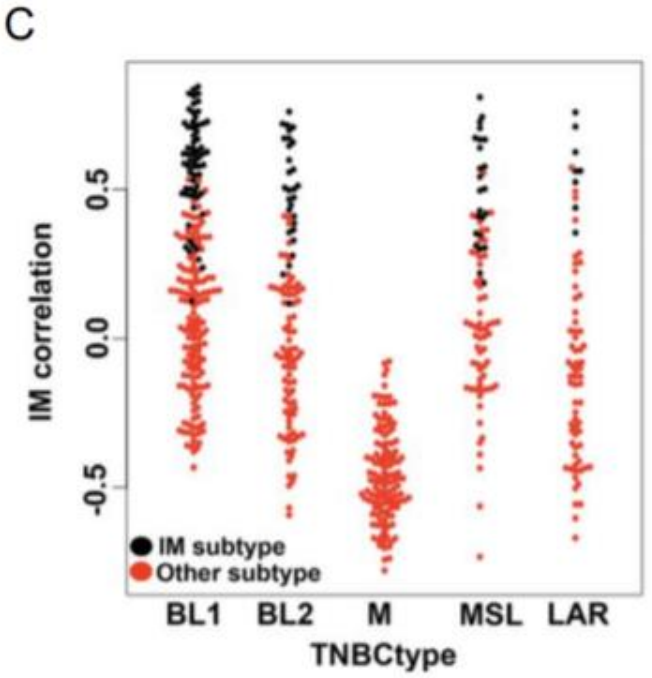


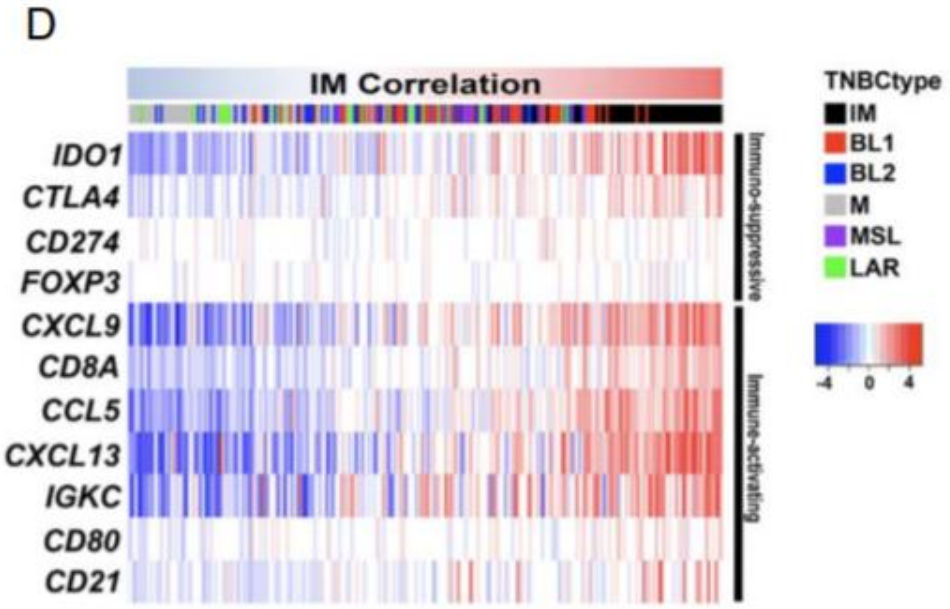
Lehmann B et al. J Clin Invest,121:2750-67, 2011

Revidovaná TNBC type-4 klasifikace

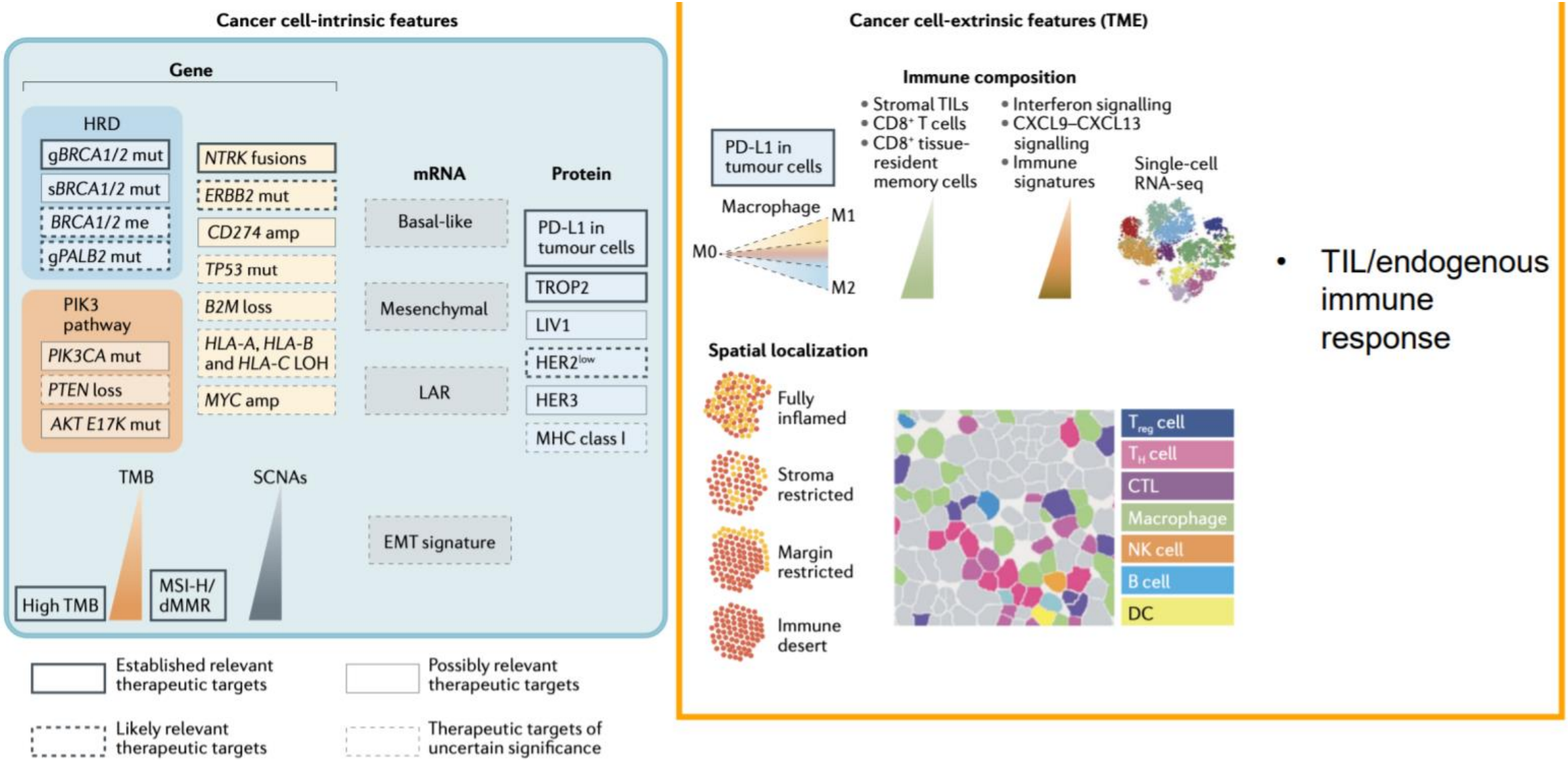








Lehmann B et al. PLOS ONE,doi:10/1371/journal.pone.0157368, 2016



Hledání relevantních cílů- BRCA 1/2 • PD-L1 • TROP2

Bianchini G, De Angelis C, Licata L, Gianni L. Treatment landscape of triple-negative breast cancer - expanded options, evolving needs. Nat Rev Clin Oncol. 2021

Jiný metastatický tropismus TNBC

Multivariate Logistic Regression for Metastatic Sites Among Newly Diagnosed TNBC
US (2010-2014)

Odds Ratio

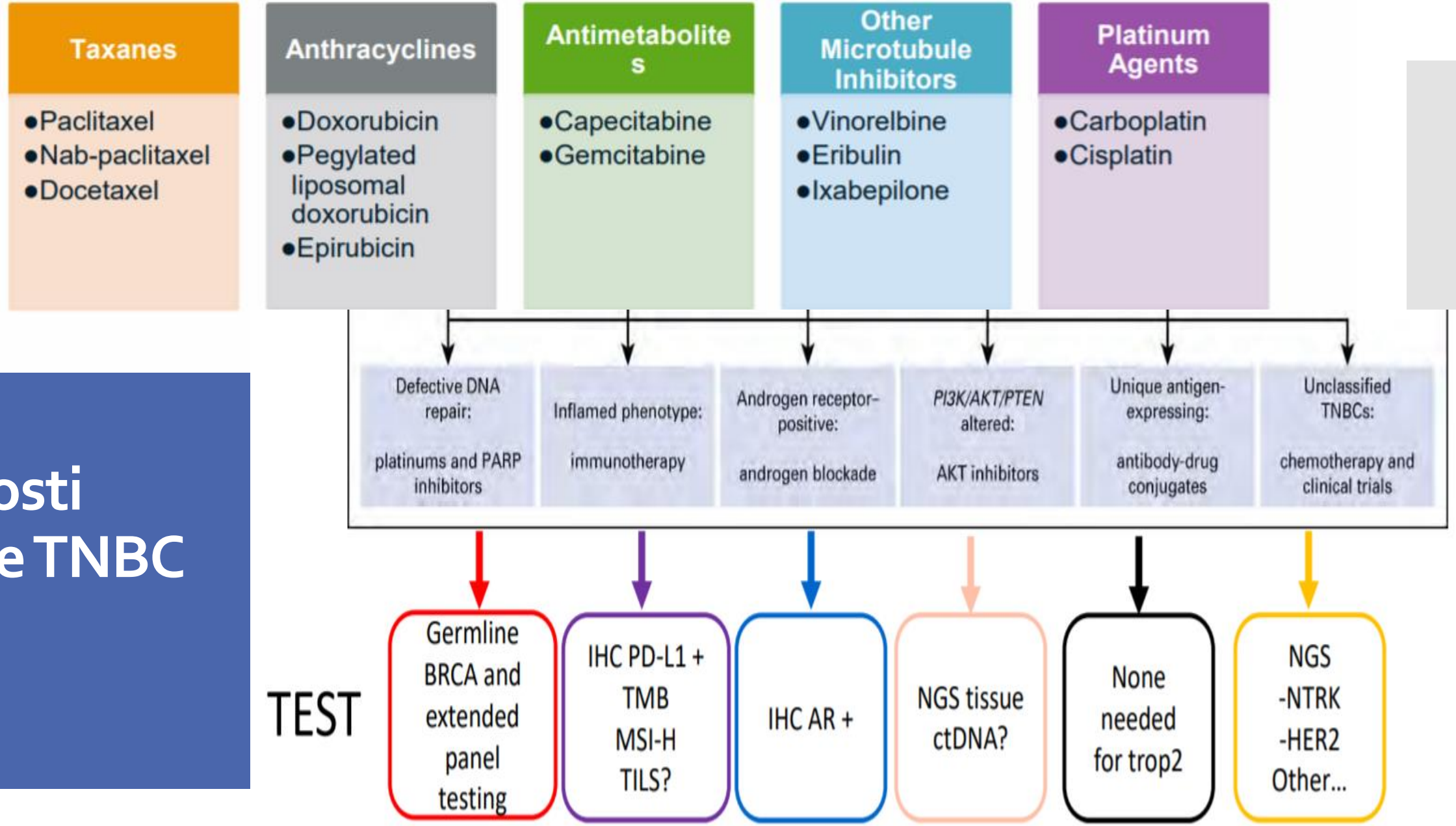
HR+/HER2- breast cancer was used as the reference point (OR = 1)

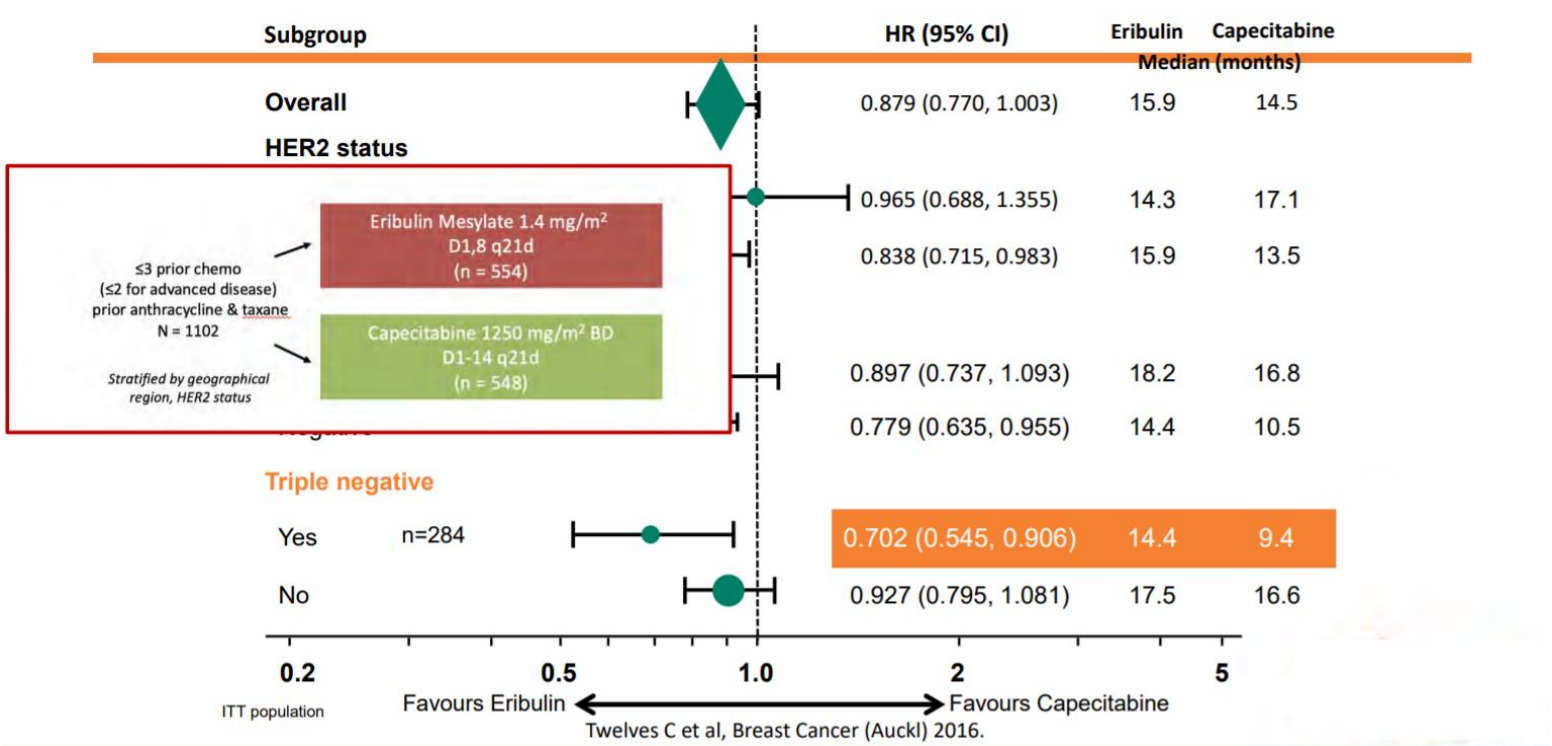
Brain	Liver	Lung	Bone
1.95	1.35	1.34	0.64
(95% CI: 1.61, 2.35)	(95% CI: 1.20, 1.51)	(95% CI: 1.21, 1.47)	(95% CI: 0.59, 0.69)

Based on analyses of SEER data including ≈ 300,000 patients with breast cancer, the brain, liver, and lung are the most frequent sites of disease recurrence amongst patients with TNBC who experience distant metastases

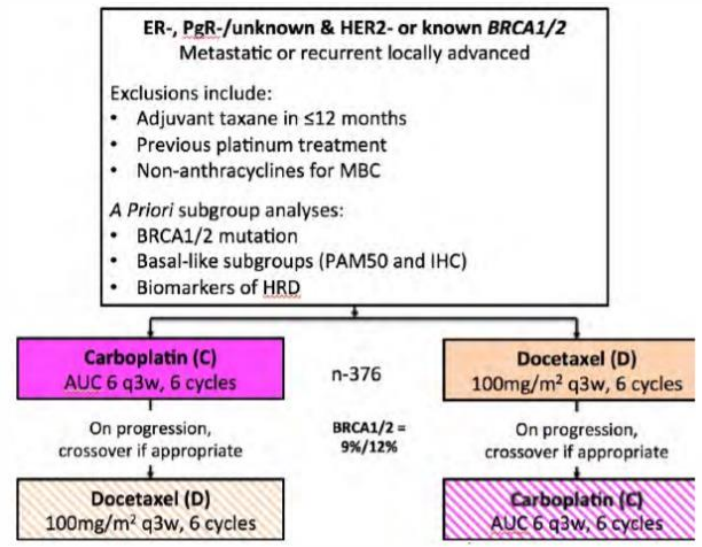
Xiao W, et al. Cancer Manag Res. 2018;10:5329-5338.

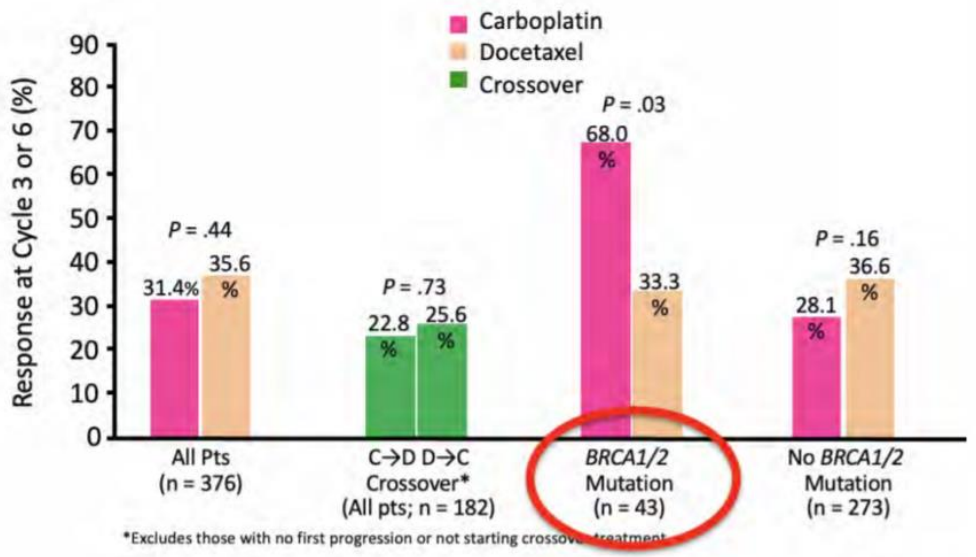
Možnosti terapie TNBC





Studie 301: capecitabine vs. eribulin u mTNBC



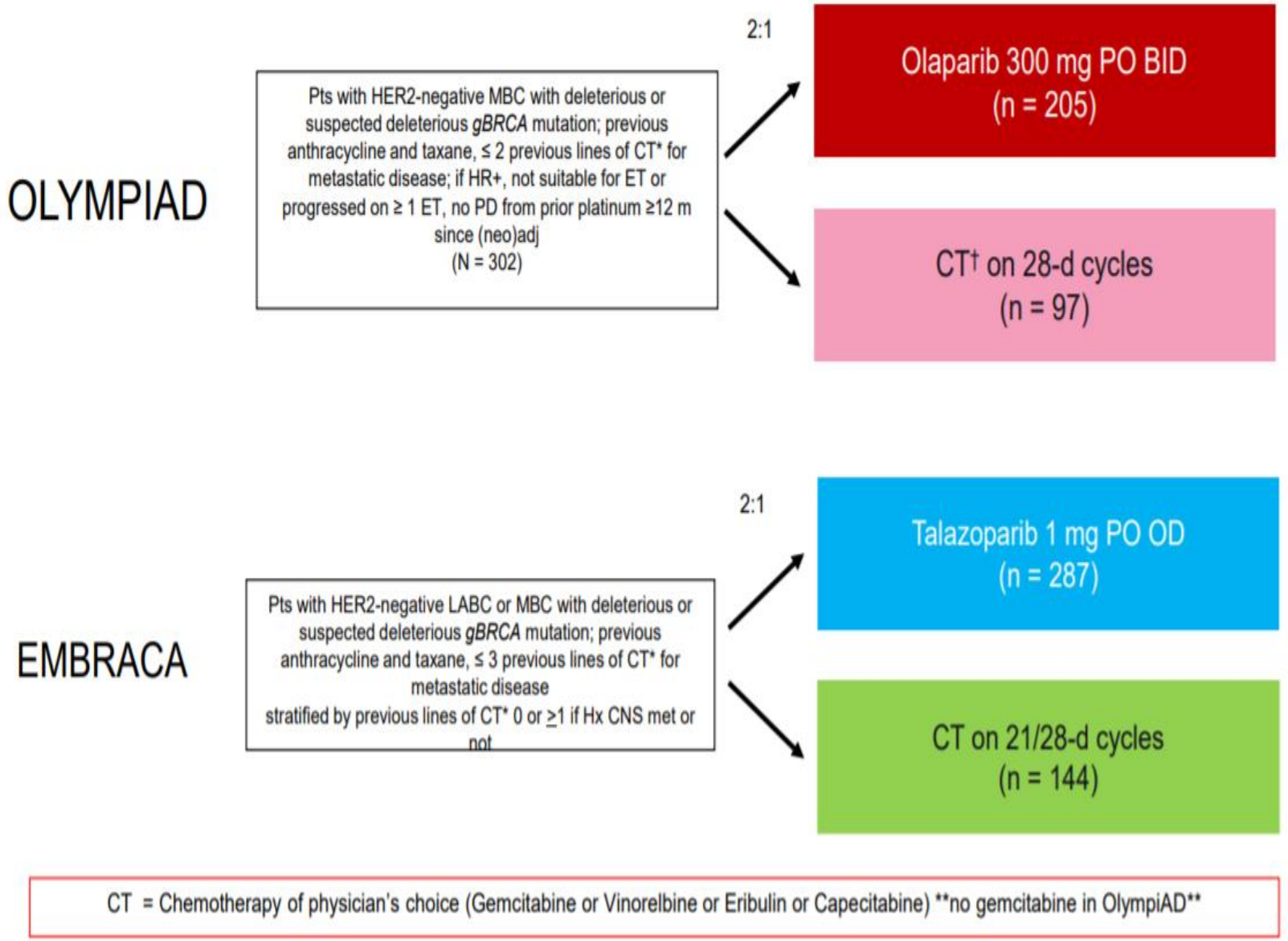


Tutt A et al, Nature Med 2018

Karboplatina vs docetaxel u TNBC s gBRCA1/2 mut

gBRCA mTNBC

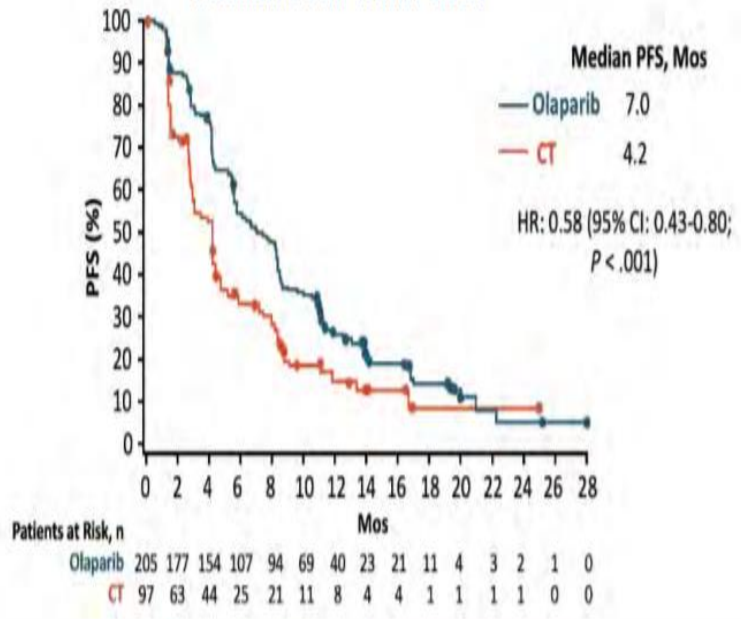
PARP inhibitors



PFS

OlympiAD: PFS by BICR (Primary Endpoint)

Robson et al. NEJM 2017

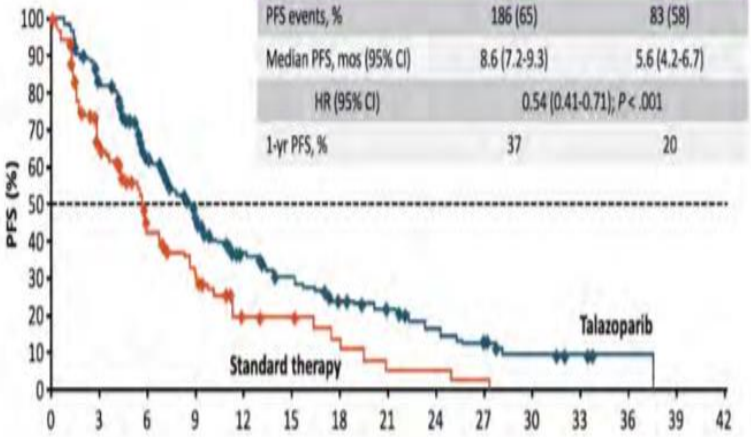


	Olaparib 300 mg bd	Chemotherapy TPC
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58 95% CI 0.43 to 0.80; P=0.0009		

EMBRACA: PFS by BICR (Primary Endpoint)

- Median follow-up time: 11.2 mos

PFS Outcome	Talazoparib (n = 287)	Standard CT (n = 144)
PFS events, %	186 (65)	83 (58)
Median PFS, mos (95% CI)	8.6 (7.2-9.3)	5.6 (4.2-6.7)
HR (95% CI)	0.54 (0.41-0.71); P < .001	
1-yr PFS, %	37	20



Litton. NEJM. 2018;379:753

Srovnání účinnosti

	Olaparib	Talazoparib
	OlympiaD (n=205)	EMBRACA (n=287)
% TNBC vs HR+	TNBC: 50% HR+: 50%	TNBC:46% HR+:54%
Median prior ctx lines for M+ % 1L mBC	na 29%	TBD 38%
Prior Platinum	29%	18%
ECOG PS 0	72%	55%
PFS (BICR)	7.0m vs. 4.2m HR=0.58 (0.43-0.80) p<0.001	8.6m vs 5.6m HR: 0.54 (95% CI: 0.41, 0.71) p<0.0001
mDOR	6.4m vs. 7.1m (BICR)	5.4m vs. 3.1m (INV)
Median time on treatment	8.3m (7.6m with tx interruption)	6.1m vs. 3.9m
ORR (BICR)	59.9% vs. 28.8%	NA
ORR (INV)	57.6% vs. 22.2%	62.6% vs. 27.2%
OS	46% maturity 19.3m vs, 19.6m HR=0.90 (0.63-1.29) p=0.57	38% maturity 22.3m vs. 19.5m HR=0.762 p=0.105

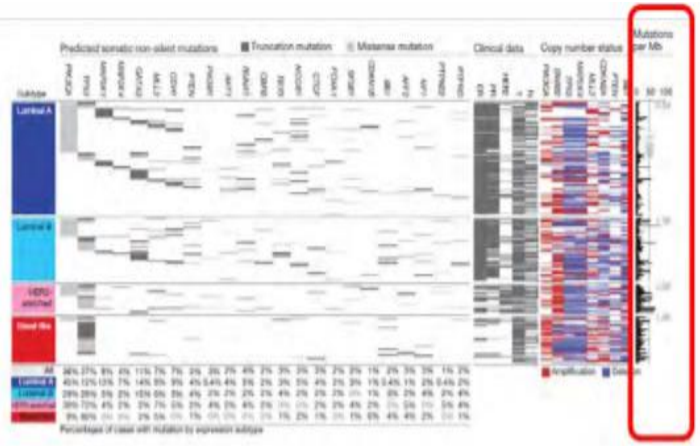
ORR = 60%

Srovnání bezpečnosti

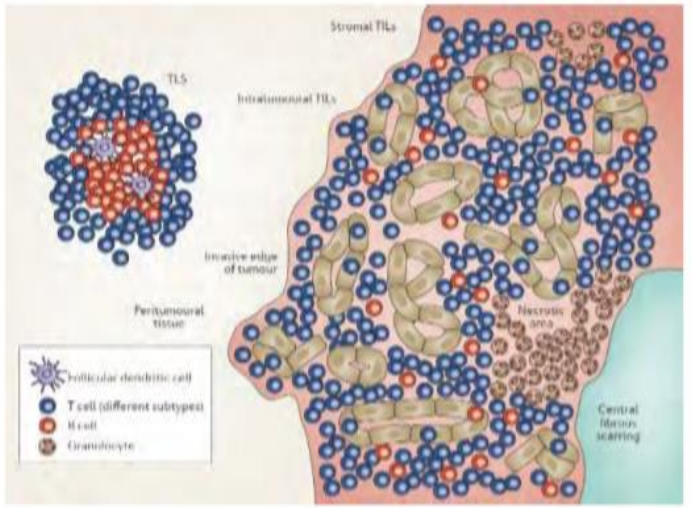
	Olaparib		Talazoparib	
	OlympiaD (n=205)		EMBRACA (n=287)	
Grade ≥3 AEs	**36.6%**		**55% (heme) /32% (non-heme)**	
Dose interruption	35%			
Dose reduction	25%			
AE leading to discontinuation	4.9% (vs. 7.7%)		7.7% (vs. 9.5%)	
SAEs	15.6% (vs. 16.6%)		31.8% (vs. 29.4%)	
AEs	all Gr	Gr≥3	all Gr	Gr≥3
Anemia	40%	**16%**	52.8%	**39.2%**
Neutropenia	27%	**9%**	34.6%	**20.9%**
Thrombocytopenia	6.8%	**1.5%**	26.9%	**14.7%**
Nausea	58%	0%	48.6%	0.3%
Vomiting	30%	0%	24.8%	2.4%
Diarrhoea	20.5%	0.5%	22%	0.7%
Liver Enzymes (AST/ALT)	9% / 11%	0% / 2%	-	-
Hypertension	0.5%		-	-
MDS/AML	-		0%	-
Fatigue	29%	2.9%	50.3%	1.7%
Alopecia	**2.9%**		**25.2%**	-
Headache	20%		32.5%	1.7%
Constipation	12.2%		22%	0.3%
Decreased appetite	16.1%		21.3%	0.3%
Back pain	11.7%	1.5%	21%	2.4%
Dyspnea	**7.8%**	**1.0%**	**17%**	**2.4%**

Proč Imunoterapie u mTNBC ?

1. **Mutační nálož** [1,2]

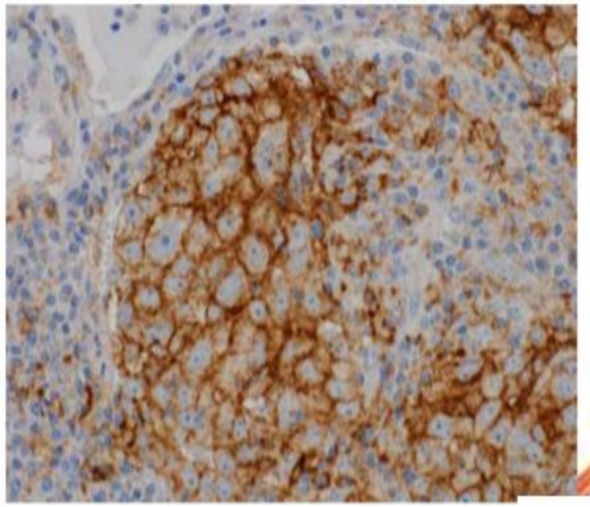


2. **TILs** [3-6]



[8]

3. **PDL1 +** [7]



1. Wang, et al. Nature 2014; 2. The Cancer Genome Atlas Network, Nature 2012; 3. Lehmann, et al. J Clin Invest 2011; 4. Cimino-Matthews, et al. Hum Pathol 2013
5. Loi, et al. Ann Oncol 2014; 6. Chen and Mellman. Immunity 2013; 7. Mittendorf, et al. Cancer Immunol Res 2014; 8. Savas P, et al. Nat Rev Clin Oncol 2016

Impassion 130

Key eligibility criteria

- Histologically documented metastatic or inoperable, locally advanced TNBC
- No prior therapy for advanced TNBC[a]
  - Prior chemotherapy including taxanes allowed in curative setting if treatment-free interval ≥ 12 mo
- ECOG PS 0-1
- Eligible for taxane monotherapy
- Tumour tissue for PD-L1 testing

(N = 902)

R 1:1

Double-blind

Atezolizumab[b] + *nab*-paclitaxel[c]

Placebo + *nab*-paclitaxel[c]

Treatment until progression or unacceptable toxicity

Stratification factors

- Liver metastases (yes vs no)
- Prior taxanes (yes vs no)
- PD-L1 status (positive vs negative)[a]

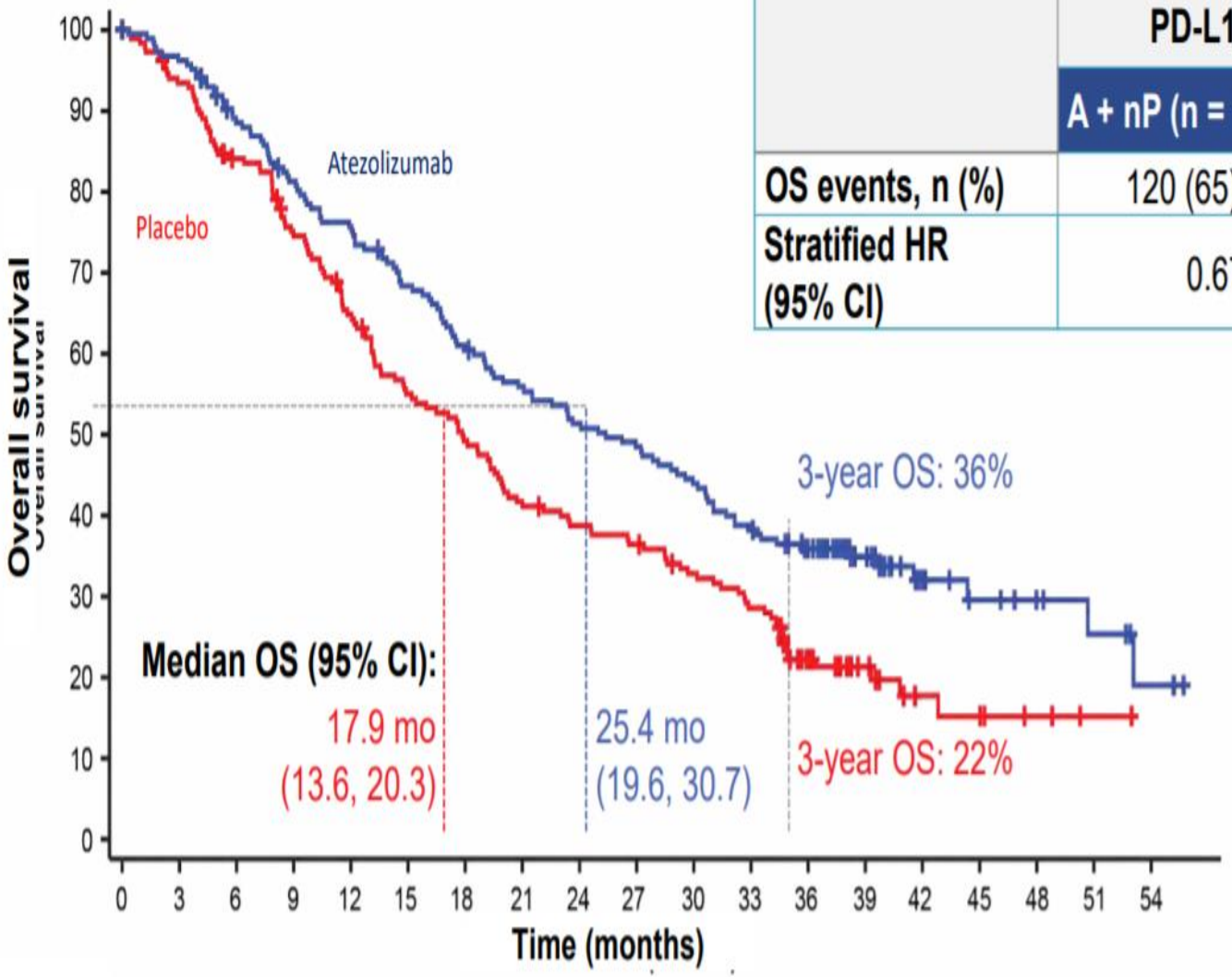
Co-primary endpoints:

- PFS[d] and OS (hierarchically tested in ITT and PD-L1 IC+ populations)

[a] PD-L1 IC ≥ 1% vs < 1% per VENTANA SP142 assay. [b] 840 mg IV on days 1 and 15 (28-day cycle). [c] 100 mg/m^2 IV on days 1, 8 and 15 (28-day cycle). [d] Per RECIST 1.1.

Schmid et al NEJM 2018
Emens LA. ESMO 2020

OS u PD-L1 IC+ populace



	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

Emens LA. Annals of Oncology 2021

Impassion 131

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

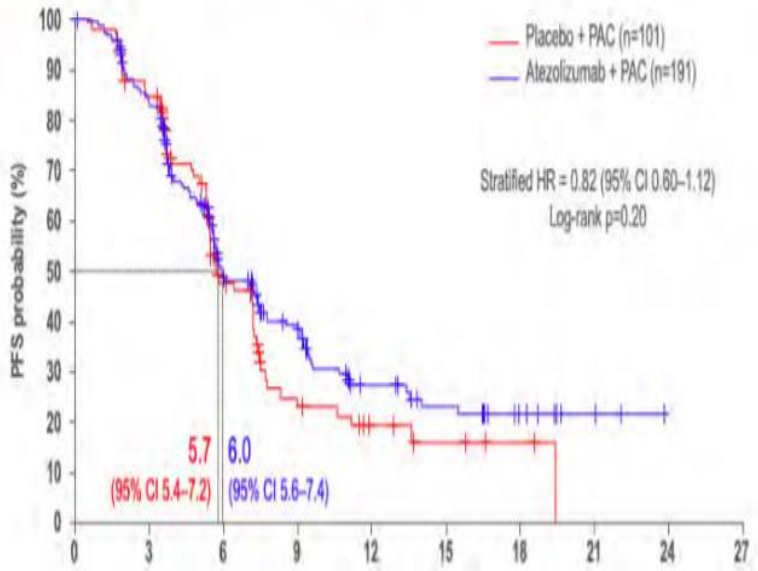
8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

VIRTUAL ESMO congress

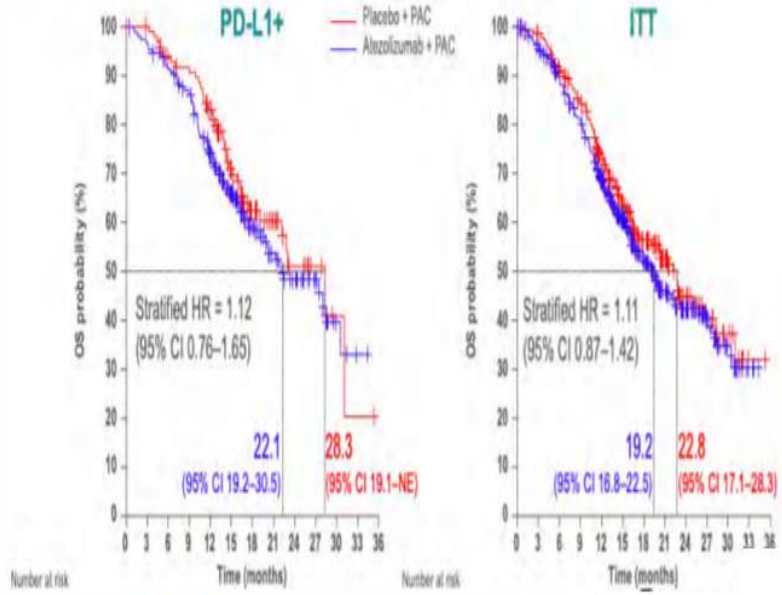
Primary analysis: PFS in the PD-L1+ population

Events in 61% of patients (data cut-off: 15 Nov 2019)



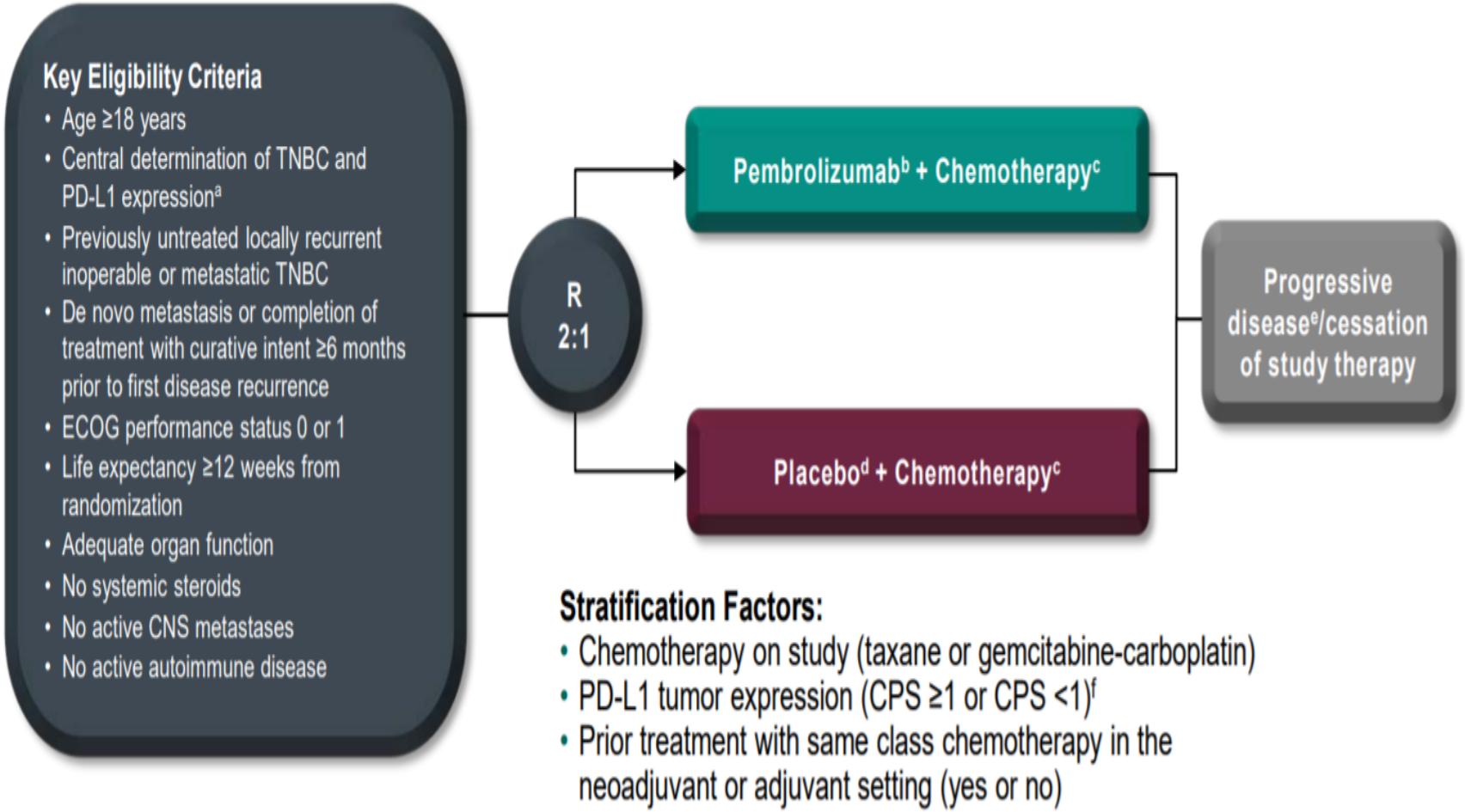
VIRTUAL ESMO congress

- Updated OS
- Data cut-off 19 Aug 2020



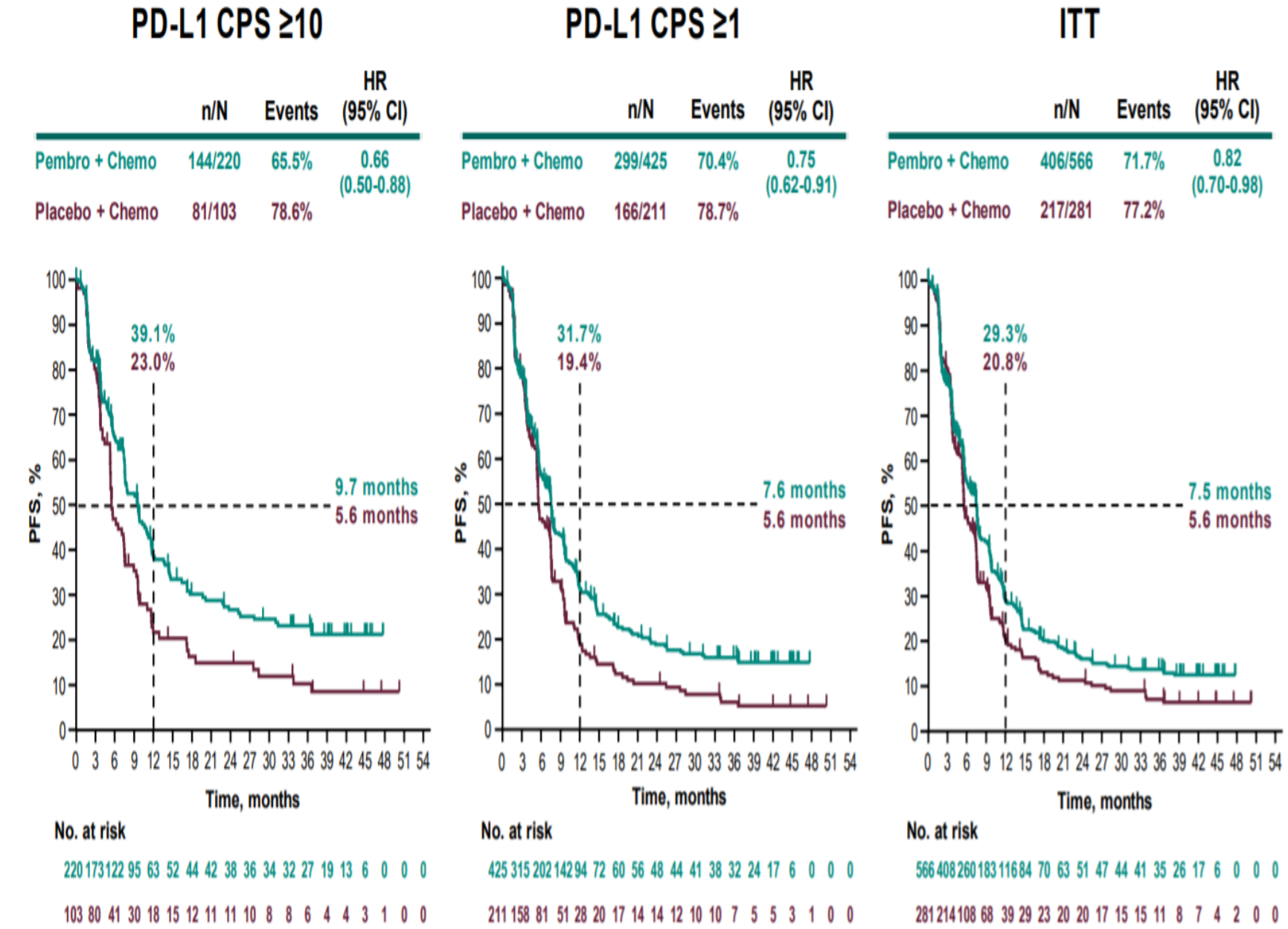
Miles et al. Annals of Oncology 2021

KEYNOTE 355


Key Eligibility Criteria
• Age ≥18 years
• Central determination of TNBC and PD-L1 expression[a]
• Previously untreated locally recurrent inoperable or metastatic TNBC
• De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
• ECOG performance status 0 or 1
• Life expectancy ≥12 weeks from randomization
• Adequate organ function
• No systemic steroids
• No active CNS metastases
• No active autoimmune disease
R
2:1
Pembrolizumab[b] + Chemotherapy[c]
Placebo[d] + Chemotherapy[c]
Progressive disease[e]/cessation of study therapy
Stratification Factors:
• Chemotherapy on study (taxane or gemcitabine-carboplatin)
• PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
• Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

Finální data PFS

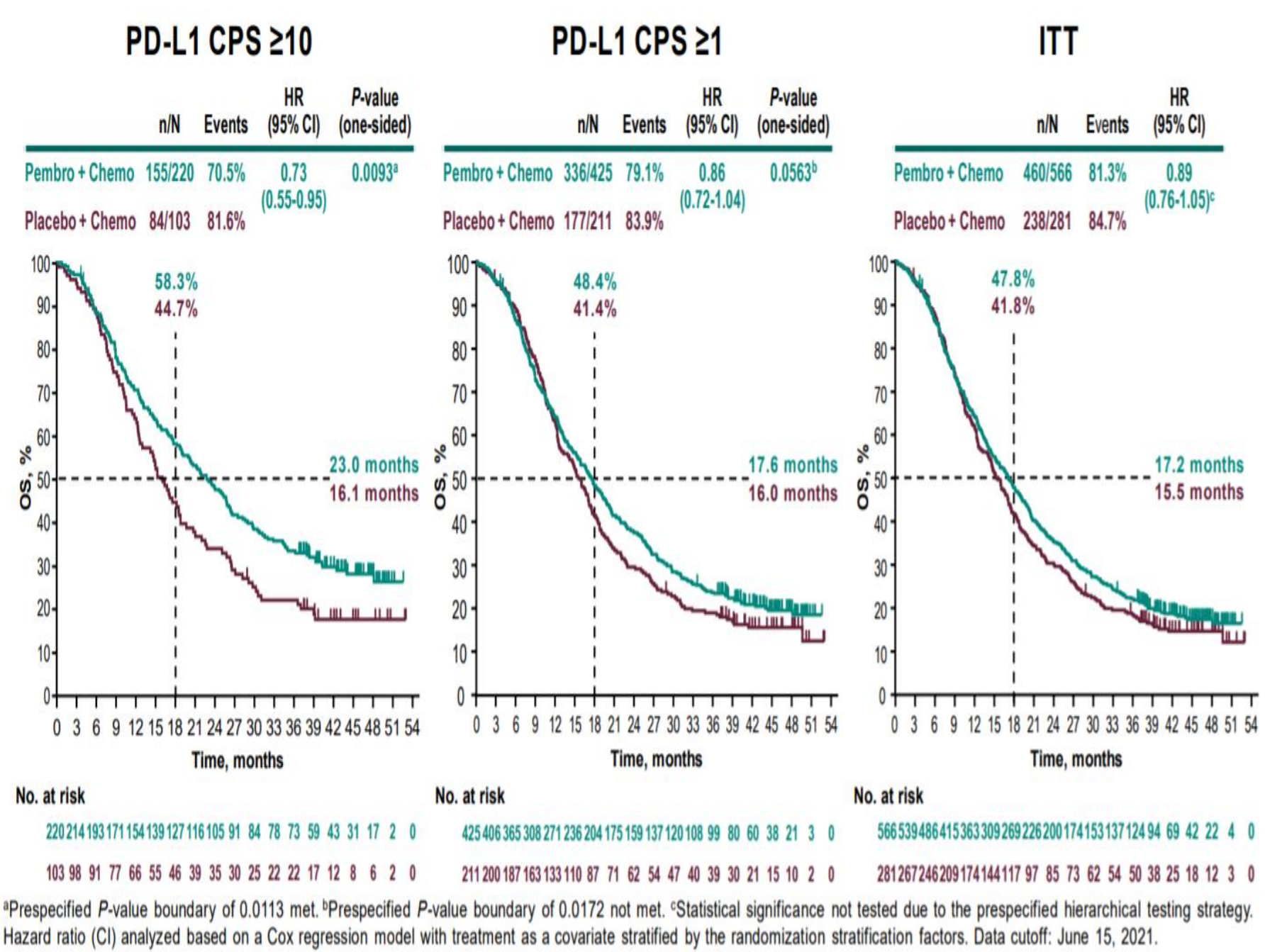
C.Cortes.
SABCS 2021



Data cutoff: June 15, 2021.

Celkové přežití, závěrečná analýza

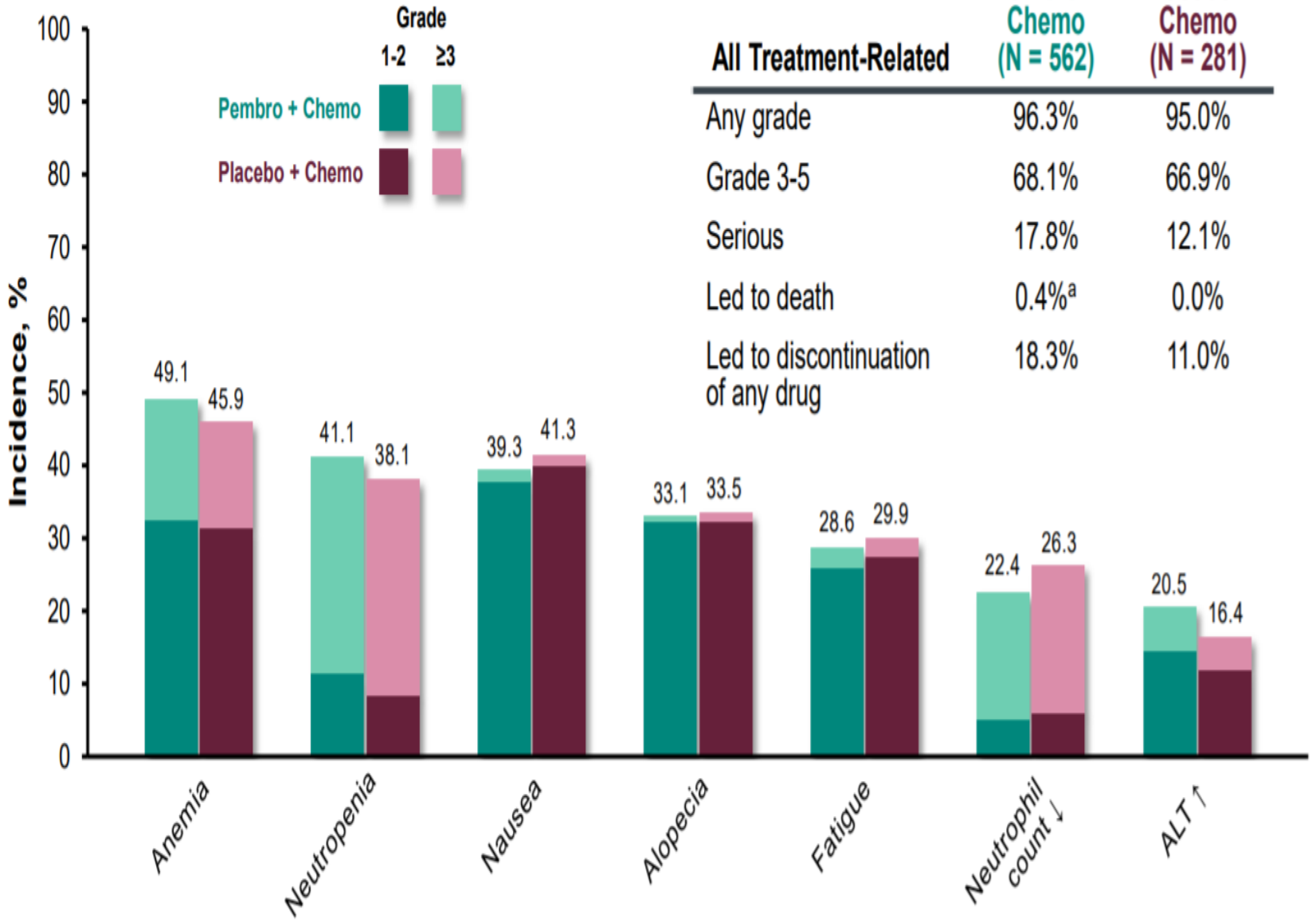
C-Cortes. SABCS 2021



[a]Prespecified *P*-value boundary of 0.0113 met. [b]Prespecified *P*-value boundary of 0.0172 not met. [c]Statistical significance not tested due to the prespecified hierarchical testing strategy. Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

Bezpečnost

C.Cortes
SABCS 2021

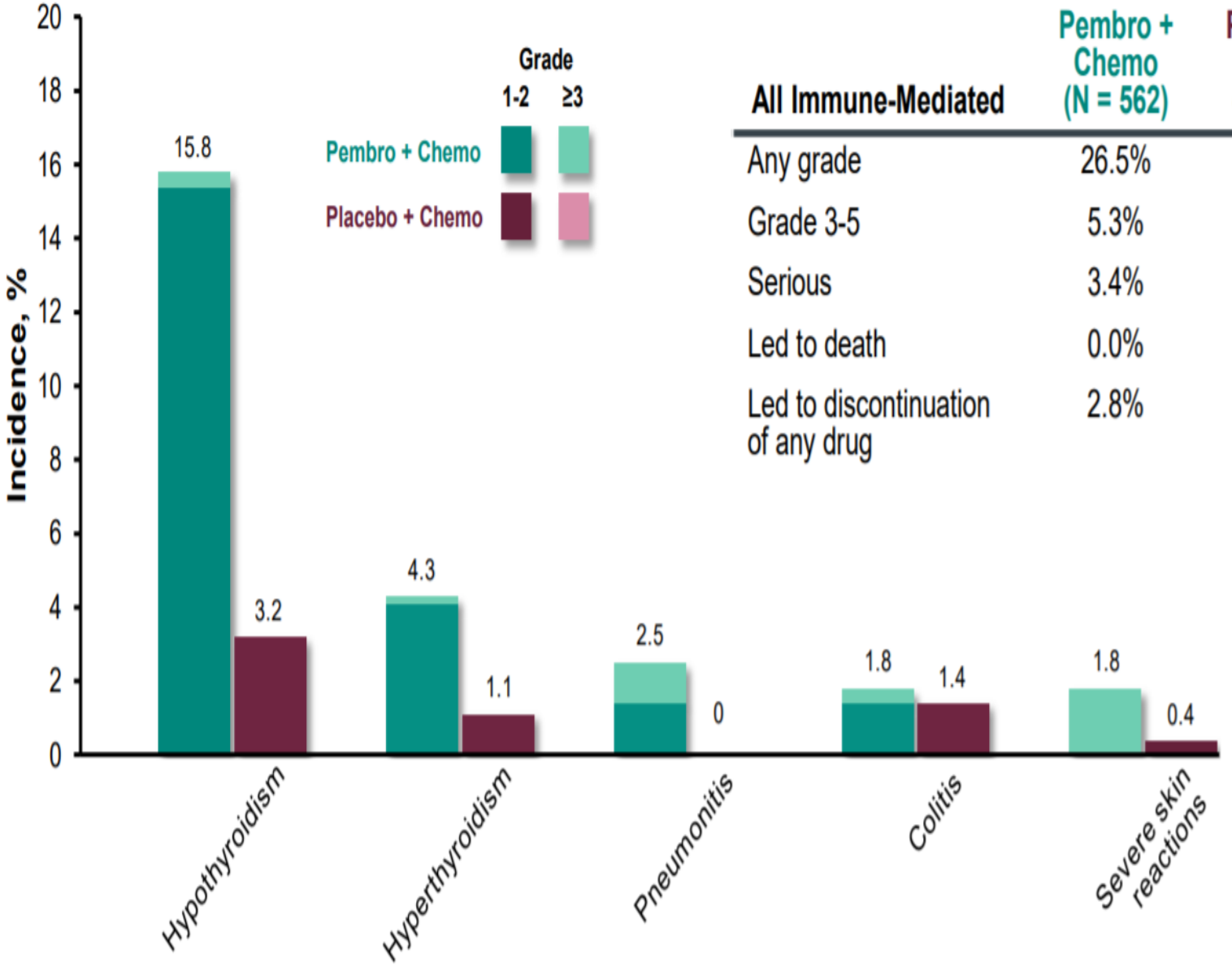


All Treatment-Related	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	96.3%	95.0%
Grade 3-5	68.1%	66.9%
Serious	17.8%	12.1%
Led to death	0.4%[a]	0.0%
Led to discontinuation of any drug	18.3%	11.0%

Treatment-Related AEs with Incidence ≥20% in Either Treatment Group

[a]1 patient from acute kidney injury and 1 patient from pneumonia. Data cutoff: June 15, 2021.

Nežádoucí účinky v souvislosti s imunitou



All Immune-Mediated	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	26.5%	6.4%
Grade 3-5	5.3%	0.0%
Serious	3.4%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	2.8%	0.0%

Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group[a]

Pembrolizumab mTNBC-KEYNOTE-355

- Výsledky podporují PD-L1 CPS ≥10 jako hraniční hodnotu pro pacienty s metastatickým TNBC, u nichž se očekává prospěch z léčby pembrolizumabem + chemoterapií
- Statisticky významné zlepšení PFS a OS při podávání pembrolizumabu + chemoterapie vs. chemoterapie samotná
- Bezpečnostní profil kombinace byl podobný jako u každého režimu jednotlivě
- Kombinovaná léčba pembrolizumab + chemoterapie by měla být považována za nový standard péče pro léčbu pacientů s lokálně recidivujícím neresekabilním nebo metastatickým TNBC s PD-L1-pozitivními tumory a CPS ≥10

Sacituzumab govitecan

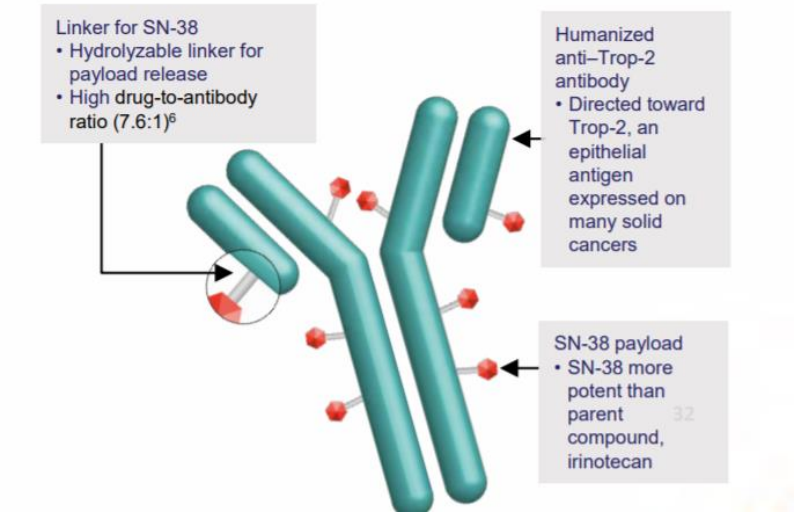
Trop-2 je exprimován ve všech podtypech karcinomu prsu a souvisí se **špatnou prognózou1,2**

- **SG** se liší od ostatních ADC

Protilátka vysoce specifická pro Trop-2- **s vysokým poměrem léku a protilátky**

Internalizace a enzymatické štěpení v nádorové buňce není nutné pro uvolnění SN-38 z protilátky-

Hydrolýza linkeru také uvolňuje SN-38 extracelulárně v nádorovém mikroprostředí



Studie fáze 3 ASCENT

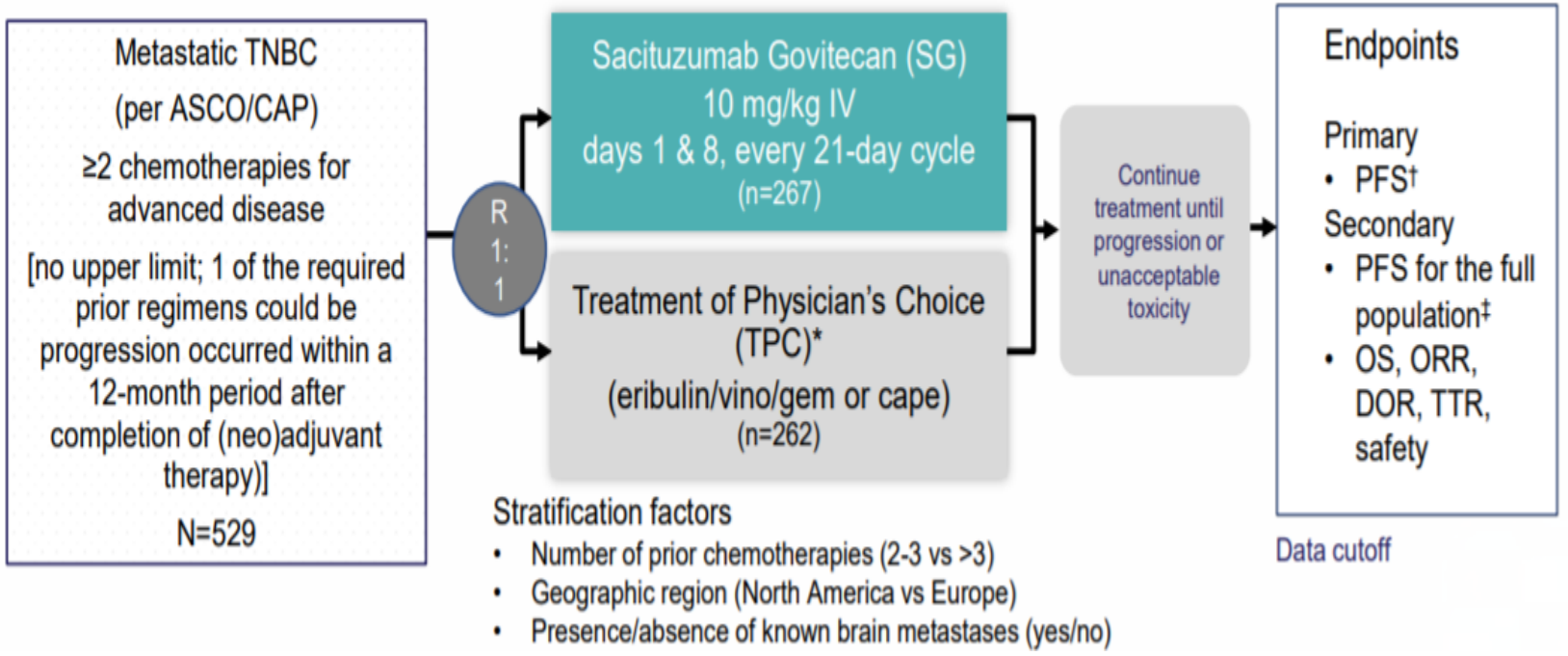
ASCENT byl předčasně zastaven kvůli přesvědčivým důkazům účinnost

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

A. Bardia, S.A. Hurvitz, S.M. Tolaney, D. Loirat, K. Punie, M. Oliveira, A. Brufsky, S.D. Sardesai, K. Kalinsky, A.B. Zelnak, R. Weaver, T. Traina, F. Dalenc, P. Aftimos, F. Lynce, S. Diab, J. Cortés, J. O'Shaughnessy, V. Diéras, C. Ferrario, P. Schmid, L.A. Carey, L. Gianni, M.J. Piccart, S. Loibl, D.M. Goldenberg, Q. Hong, M.S. Olivo, L.M. Itri, and H.S. Rugo, for the ASCENT Clinical Trial Investigators*



Demografie a pacienti

	SG (n=235)	TPC (n=233)
Female—no. (%)	233 (99)	233 (100)
Median age—yr (range)	54 (29-82)	53 (27-81)
Race or ethnic group—no. (%)		
White	188 (80)	181 (78)
Black	28 (12)	28 (12)
Asian	9 (4)	9 (4)
Other or not specified	10 (4)	15 (6)
ECOG PS—no. (%)		
0	108 (46)	98 (42)
1	127 (54)	135 (58)
BRCA 1/2 mutational status—no. (%)		
Positive	16 (7)	18 (8)
Negative	133 (57)	125 (54)
Unknown	86 (37)	90 (39)
TNBC at initial diagnosis*		
Yes	165 (70)	157 (67)
No	70 (30)	76 (33)

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Previous PARP inhibitor—no. (%)	17 (7)	18 (8)
Previous use of checkpoint inhibitors—no. (%)	67 (29)	60 (26)
Most common sites of disease¶—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

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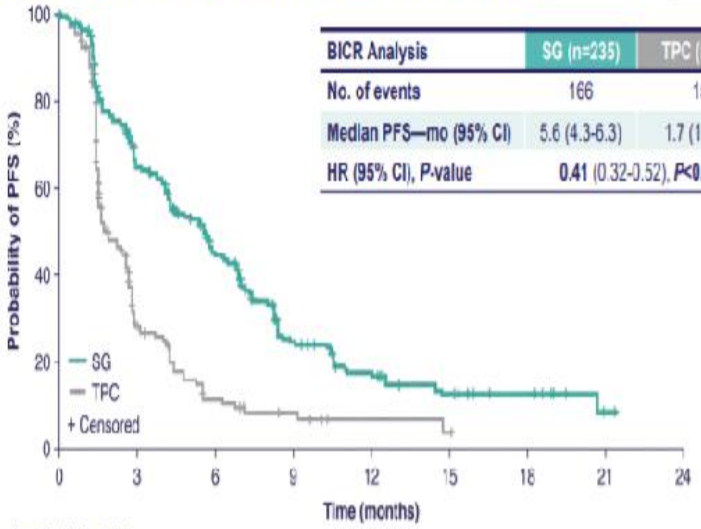
PFS + OS

Progression-Free Survival (BICR Analysis)



BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Number of patients at risk

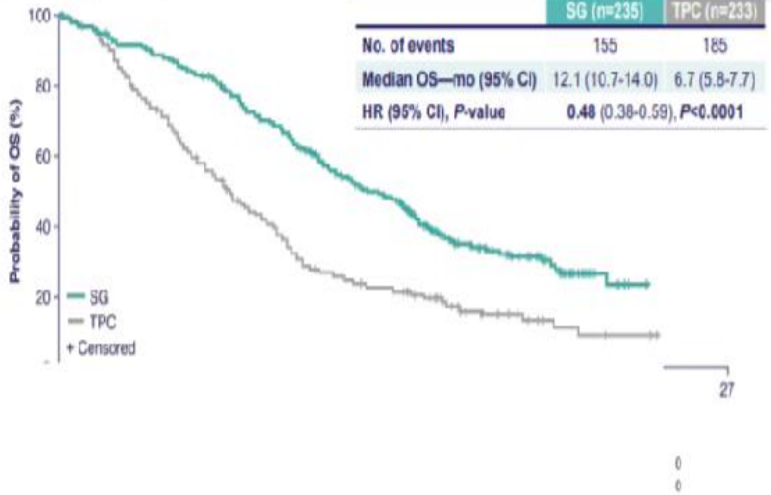
SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	?																				

Primary endpoint (PFS) assessed by indepe
Secondary endpoint (PFS) assessed in the I
BICR, blind independent central review; PFS

4 months benefit
median PFS

± 5.5 months benefit
median OS

Overall Survival



	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

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Nežádoucí účinky v souvislosti s léčbou -TRAEs

		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	Neutropenia†	63	46	17	43	27	13
	Anemia‡	34	8	0	24	5	0
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	Diarrhea	59	10	0	12	<1	0
	Nausea	57	2	<1	26	<1	0
	Vomiting	29	1	<1	10	<1	0
Other	Fatigue	45	3	0	30	5	0
	Alopecia	46	0	0	16	0	0

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

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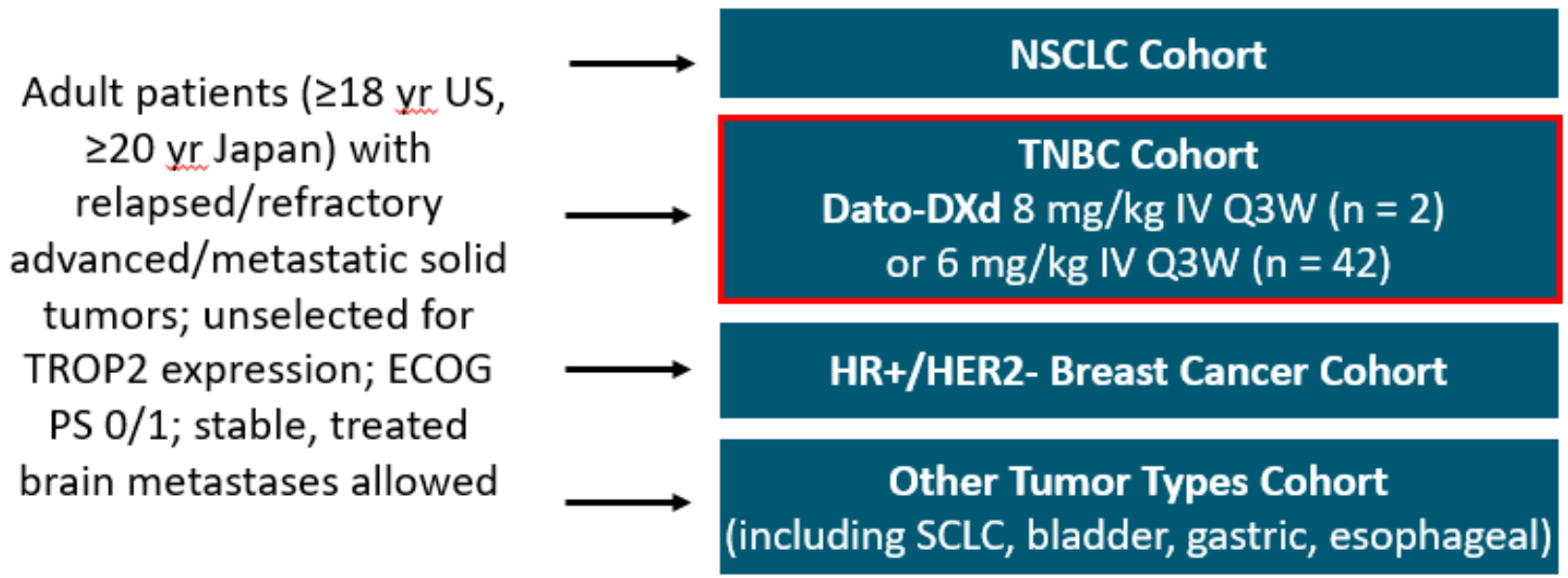
TROPION-PanTumor01: Studie fáze I s Datopotamabem Deruxtecanem u mTNBC a jiných metastatických solidních tumorů

- multikohortní studie fáze I, eskalace dávky a expanze; TNBC kohorta 44 pac.
- Dato-DXd: nový ADC zacílený na TROP2 + inhibitor topoizomerázy I



- Primary objectives
  - bezpečnost
  - Tolerabilita
- Secondary objectives
  - účinek
  - PK
  - Protilátky proti léku

- Medián sledování pro kohortu TNBC: 7,6 měsíce (rozsah: 4–13)

Krop. SABCS 2021. Abstr GS1-05.

TROPION-PanTumor01: Závěry

- Dato-DXd prokázal významnou a trvalou účinnost u silně předléčených pacientů s TNBC
- ORR 34 % v celé kohortě TNBC
- ORR 52 % u pacientů s TNBC, kteří dosud nebyli léčeni ADC na bázi inhibitoru topoizomerázy I
- Dato-DXd měl zvládnutelný bezpečnostní profil
- Vyšetřovatelé dospěli k závěru, že další studie Dato-DXd u rakoviny prsu je oprávněná
- BEGONIA: probíhající studie fáze Ib/II hodnotící účinnost a bezpečnost durvalumabu plus Dato-DXd nebo jiných nových látek u metastatického TNBC (NCT03742102)
- TROPION-Breast01: probíhající studie fáze III u HR+/HER2- rakoviny prsu (NCT05104866)
- Plánovaná studie fáze III v TNBC

Krop. SABCS 2021. Abstr GS1-05.

Současný léčebný algoritmus mTNBC

Dle ESMO Guidlines 2021

Testování biomarkerů		
Biomarkery	pozitivní	negativní
	PD-L1+ (SP142 or 22C3) **gBRCA+**	**PD-L1-** (SP142 or 22C3) **gBRCA-** **Klinické studie** **NGS**
1.linie	**PD-L1** +: nab-paclitaxel + atezolizumab , gem/carbo + pembrolizumab **gBRCA**+: PARP inhibitor. platinová CHT **Pokud oba +,** není evidence co je lepší	**PDL1** – nebo **gBRCA-** chemotherapie – *CHT (chemotherapie+ bevacizumab)
2.linie	**gBRCA+** : PARP inhibitor nebo platinová CHT(pokud nebyla v 1,linii) *CHT, Sacituzumab govitecan	**gBRCA**-: *CHT Sacituzumab govitecan
3.linie	Sacituzumab govitecan *CHT	Sacituzumab govitecan *CHT
	TMB high, MSI- H: mono pembrolizumab **NTRK fusion: Larotrectinib/entrectinib**	**TMB high, MSI- H: mono pembrolizumab** **NTRK fusion: Larotrectinib/entrectinib**

*CHT- taxane/platinum/eribulin/capecitabine/adriamycin/navelbine/CMF

Přihlášky :
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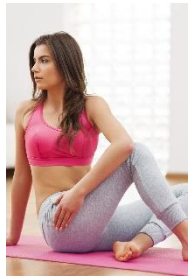

KONDICÍ PROTI RAKOVINĚ

PROJEKT 35

Spolupráce **Projektu 35, který projekt zastřešuje, Onkologické kliniky VFN + 1.LF, 3.interní kliniky VFN a 1.LF UK, Ústavu tělovýchovného lékařství 1.LF UK a pacientských organizací**

Zařazení **30 nemocných s metastatickým karcinomem prsu, se stabilizací nemoci, PS0, s doporučením ošetřujícího onkologa, nejraději z Prahy a okolí.**

4 měsíční program **pod přísnou kontrolou lékaře** od 3/22

S cílem **aktivně zapojit nemocné** do zlepšování celkového stavu, zlepšení kvality života, zlepšení psychické kondice a třeba i prodloužení života.